Contribution ID: **95** Type: **not specified**

PARP-1 targeted alpha-emitting radiotherapeutics: an examination of potential toxicity

Introduction: Radiolabeling poly-ADP ribose polymerase 1 (PARP-1) inhibitors potentially enables targeted delivery of alpha-emitting isotopes directly to cancer cells overexpressing PARP-1. However, there is concern for bone marrow toxicity due to its intrinsically high PARP-1 expression. Therefore, we examined bone marrow toxicity at therapeutically relevant doses of an astatine-211 labeled PARP-1 inhibitor, [211At]MM4.

Methods: Male and female C57BL6 mice received 0, 12, 24, and 36 MBq/kg of [211At]MM4 and then were sacrificed after 24 hours, 2 weeks, and 4 weeks. The red marrow-containing femur was harvested and was analyzed with colony formation assay, immunofluorescent (IF) microscopy, histopathology, and immunohistochemistry (IHC). Peripheral blood samples were analyzed for complete blood count (CBC). Additionally, we performed [211At]MM4 biodistribution assay on another set of 20 C57BL6 mice at post-injection time points of 5, 30, 60, 180, and 360 minutes. With the biodistribution data, OLINDA/EXM v1.1 was used for radiation dosimetry calculations in reference to human pediatric models.

Results: The CBC revealed significant lymphopenia only in the 2-week group treated with 24 MBq/kg. A slight decrease in lymphocyte percentage was observed in the 24 MBq/kg mice at 2 weeks and the 36 MBq/kg at 2 and 4 weeks. Significant neutrophilia was observed in all 2-week groups, as well as the 4-week group treated at 36 MBq/kg. Colony formation assay revealed no reduction, but rather significant increase in granulocyte, macrophage, and burst forming unit-erythroid colonies. Histopathology revealed maintained bone marrow cellularity across the treatment groups. IF and IHC demonstrated heterogeneous PARP-1 expression in the bone marrow. The biodistribution and subsequent dosimetry calculations found significantly higher, but nonlethal organ radiation dose per injected activity levels in the red bone marrow, spleen, and thyroid in both 1 and 5-year-old human models.

Conclusion: Overall, the results suggest that doses up to 36 MBq/kg of [211At]MM4 can be administered to C57BL6 mouse models without producing significant systemic or bone marrow toxicity. These results provide promising developments for understanding toxicity associated with the alpha-emitting compound [211At]MM4 *in vivo*. Future studies using fractionated dosing regimens in pre-clinical tumor models will evaluate therapeutic efficacy and further evaluate associated toxicities.

Email Address

adamamansfield@gmail.com

Presentation Type

Contributed Oral

Primary author: MANSFIELD, Adam (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.)

Co-authors: Dr PAWEL, Bruce R. (Department of Pathology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.); HOU, Catherine (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); Dr PRYMA, Daniel A. (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); Dr MARTINEZ, Daniel (Department of Pathology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.); Dr LEE, Hwan (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); VERDONE, James (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); Dr MARIS, John M. (Division of Oncology and Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Colket Translational Research Building, 3501 Civic Center Boulevard,

Philadelphia, PA 19104, USA; Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); RATHI, Komal S. (Division of Oncology and Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Colket Translational Research Building, 3501 Civic Center Boulevard, Philadelphia, PA 19104, USA; Department of Biomedical and Health Informatics and Center for Data-Driven Discovery in Biomedicine, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.); Dr MAKVANDI, Mehran (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); Dr SAMANTA, Minu (Division of Oncology and Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Colket Translational Research Building, 3501 Civic Center Boulevard, Philadelphia, PA 19104, USA; Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); BURRELL, Paige E. (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); Dr RAMAN, Pichai (Division of Oncology and Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Colket Translational Research Building, 3501 Civic Center Boulevard, Philadelphia, PA 19104, USA; Department of Biomedical and Health Informatics and Center for Data-Driven Discovery in Biomedicine, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.); Dr MACH, Robert H. (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); Dr CARLIN, Sean D. (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.)

Presenter: MANSFIELD, Adam (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.)